FORM PTO-1390 (Modified) (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 065691/0215

09/806834

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): Unassigned

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR99/02375	October 5, 1999	October 5, 1998

TITLE OF INVENTION: COSMETIC METHOD FOR PREVENTING AND/OR TREATING SKIN STRETCHMARKS, AND USE IN DERMATOLOGY

APPLICANT(S) FOR DO/EO/US: Philippe MSIKA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. ☐ Applicant claims small entity status under 37 CFR 1.27 .

Items 12. to 17. below concern other document(s) or information included:

12. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
14. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☒ Other items or information: Associate Power of Attorney (1 page).

JC08 Rec'd PCT/PTO 05 APR 2001

U.S. APPLICATION NO (If known, see 37 C.F.R. 1.50) Unassigned 09/806834	INTERNATIONAL APPLICATION NO. PCT/FR99/02375	ATTORNEY'S DOCKET NUMBER 065691/0215

18. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO $860.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))		

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate	CALCULATIONS	PTO USE ONLY
Total Claims	15	-	20	=	0	×	$18.00	$0.00	
Independent Claims	1	-	3	=	0	×	$80.00	$0.00	
Multiple dependent claim(s) (if applicable)							$270.00	$860.00	

	CALCULATIONS	PTO USE ONLY
TOTAL OF ABOVE CALCULATIONS =	$860.00	
Reduction by ½ for filing by small entity, if applicable.	$0.00	
SUBTOTAL =	$860.00	
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +		
TOTAL NATIONAL FEE =	$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$40.00	
TOTAL FEES ENCLOSED =	$900.00	
Amount to be: refunded	$	
charged	$	

a. ☒ A check in the amount of $900.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $1170.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Foley & Lardner
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109

Phillip J. Articola
SIGNATURE

Phillip J. Articola
for NAME STEPHEN B. MAEBIUS
Reg. No. 38,819

REGISTRATION NUMBER 35,264

09806834 . 040501

Atty. Dkt. No. 065691/0215

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Philippe Msika

Entitled: COSMETIC METHOD FOR PREVENTING AND/OR TREATING SKIN STRETCHMARKS, AND USE IN DERMATOLOGY

Serial No. To be assigned

Filing Date April 5, 2001

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the present application, Applicant's respectfully requests that the above-identified application be amended as follows:

In the Claims:

In accordance with 37 C.F.R. § 1.121(c) (3), please substitute for pending claims 3-5, 7-10, and 12-15 with the following clean version of the claims. The changes to these claims are shown explicitly in the attached "Marked Up Version of Claims."

3. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the anti-stretchmark agent is chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP®, and mixtures of these peptides.

4. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the proportion of anti-stretchmark agent is between about 0.1% and about 10% by weight relative to the total weight of the composition.

5. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the composition also comprises at least one a-hydroxy acid, in combination with the anti— stretchmark agent.

7. (Amended) Cosmetic prevention and/or treatment method according to Claim 5, characterized in that the proportion of a-hydroxy acid is between about 0.1% and about 20% by weight relative to the total weight of the composition.

8. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the composition comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren—CPP® and mixtures of these peptides, in combination with lactic acid.

9. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the composition also comprises a compound for adjusting the pH to a value of between about 2 and about 4.

10. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the composition also comprises at least one substance-P and neuropeptide-Y inhibitor compound.

12. (Amended) Cosmetic prevention and/or treatment method according to Claim 10, characterized in that the proportion of substance-P and neuropeptide-Y inhibitor compound is between about 0.1% and about 5% by weight relative to the total weight of the composition.

13. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the composition comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren_CPP® and mixtures of these peptides, in combination with lactic acid and *Enteromorpha compressa*

14. (Amended) Cosmetic prevention and/or treatment method according to Claim 1, characterized in that the composition also comprises at least one compound chosen from the group consisting of extract of *Sophora japonica,* methylsilaryl lactate, copper gluconate and zinc gluconate, and mixtures of these compounds.

15. (Amended) Use of a composition as defined in Claim 1, to prepare a dermatological medicinal product for preventing and/or treating skin stretchmarks.

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application.

Respectfully submitted,

Date April 5, 2001

By Phillip J. Antonello Reg. No. 38,819

for / Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5571
Facsimile: (202) 672-5399

MARKED UP VERSION OF AMENDED CLAIMS

3. Cosmetic prevention and/or treatment method according to Claim 1 [or 2], characterized in that the anti-stretchmark agent is chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP®, and mixtures of these peptides.

4. Cosmetic prevention and/or treatment method according to [any one of Claims] Claim 1 [to 3], characterized in that the proportion of anti-stretchmark agent is between about 0.1% and about 10% by weight relative to the total weight of the composition.

5. Cosmetic prevention and/or treatment method according to [any one of Claims] Claim 1 [to 4], characterized in that the composition also comprises at least one a-hydroxy acid, in combination with the anti— stretchmark agent.

7. Cosmetic prevention and/or treatment method according to Claim 5 [or 6], characterized in that the proportion of a-hydroxy acid is between about 0.1% and about 20% by weight relative to the total weight of the composition.

8. Cosmetic prevention and/or treatment method according to [any one of the preceding claims] Claim 1, characterized in that the composition comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren—CPP® and mixtures of these peptides, in combination with lactic acid.

9. Cosmetic prevention and/or treatment method according to [any one of the preceding claims] Claim 1, characterized in that the composition also comprises a compound for adjusting the pH to a value of between about 2 and about 4.

10. Cosmetic prevention and/or treatment method according to [any one of the preceding claims] Claim 1, characterized in that the composition also comprises at least one substance-P and neuropeptide-Y inhibitor compound.

12. Cosmetic prevention and/or treatment method according to Claim 10 [or 11], characterized in that the proportion of substance-P and neuropeptide-Y inhibitor compound

is between about 0.1% and about 5% by weight relative to the total weight of the composition.

13. Cosmetic prevention and/or treatment method according to [any one of the preceding claims] Claim 1, characterized in that the composition comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren_CPP® and mixtures of these peptides, in combination with lactic acid and *Enteromorpha compressa*

14. Cosmetic prevention and/or treatment method according to [any one of the preceding claims] Claim 1, characterized in that the composition also comprises at least one compound chosen from the group consisting of extract of *Sophora japonica,* methylsilaryl lactate, copper gluconate and zinc gluconate, and mixtures of these compounds.

15. Use of a composition as defined in [any one of Claims] Claim 1 [to 14], to prepare a dermatological medicinal product for preventing and/or treating skin stretchmarks.

COSMETIC METHOD FOR PREVENTING AND/OR TREATING SKIN STRETCHMARKS, AND USE IN DERMATOLOGY

The present invention relates to a cosmetic method for preventing and/or treating skin stretchmarks, and to the use of a composition to prepare a dermatological medicinal product for preventing and/or treating stretchmarks.

Stretchmarks are visible marks on the skin resulting from the skin being stretched due to a gain in weight or mechanical stresses, which usually concern women, after puberty or a first pregnancy. About 50% of pregnant women develop stretchmarks, on the thighs, the abdomen and/or the breasts. Stretchmarks may also appear during physiological or pathological states such as obesity, tuberculosis and typhoid fever, and also during a relatively intensive dietary regime.

The treatment of stretchmarks has been described, for example, in the article by P. Zheng et al., "Anatomy of striae", British Journal of Dermatology 112:185-193 (1985), in which it is especially reported that stretchmarks are scars resulting from an inflammation process which destroys elastic fibers.

Since then, many compounds have been proposed as active principles for treating stretchmarks, such as, for example, tretinoin (or all-trans-retinoic acid). According to the article by R.E.B. Watson et al., "Fibrillin microfibrils are reduced in skin exhibiting striae distensae", British Journal of Dermatology 138:931-937 (1998), it would appear that tretinoin has an anti-stretchmark action with a tendency toward essentially restoring the network of fibrillins, which are the main constituent of the microfibrils within elastic fibers, when compared with other constituents of the extracellular matrix.

However, although the active compounds of the prior art produce a stretchmark-regressing effect, it

nevertheless remains that the results obtained are not entirely satisfactory, in particular given the well-known skin intolerance problem of tretinoin. There has thus hitherto been a real demand for the development of a product for efficiently preventing and/or treating, with acceptable skin tolerance, this complex and particularly unattractive problem of stretchmarks.

It has now been found, entirely surprisingly and unexpectedly, that the use of certain peptides makes it possible entirely significantly to prevent and/or treat skin stretchmarks, in a manner which is acceptable as regards skin tolerance.

A subject of the present invention is thus a cosmetic method for preventing and/or treating skin stretchmarks, characterized in that a composition is applied to the areas of skin liable to form or comprising stretchmarks, this composition comprising, in a suitable vehicle, at least one anti-stretchmark agent chosen from the group consisting of soya peptides and tripeptides consisting of the amino acids glycine, histidine and lysine, and mixtures of these peptides.

According to the present invention, the expression "prevention of skin stretchmarks" means an action which prevents or at least reduces the formation of stretchmarks, i.e. their length, width and/or depth, in the context of a cosmetic or dermatological treatment, by applying the composition before and during an event known to cause the appearance of stretchmarks, such as pregnancy. According to the present invention, the expression "treatment of skin stretchmarks" means an action which visibly and measurably regresses, i.e. resorbs, in the context of a cosmetic or dermatological treatment, already-formed stretchmarks, i.e. their length, width and/or depth.

Thus, the composition used according to the invention may be applied to areas of skin liable to form stretchmarks, comprising stretchmarks in the process of being formed or even comprising already-formed stretchmarks.

The soya peptides in the composition used according to the present invention may be any peptide obtained by hydrolysis of proteins extracted from soya, under operating conditions known to those skilled in the art, in other words any soya protein hydrolysate. These soya peptides are preferably peptides which have also undergone a fermentation with a strain of microorganism. In general, a fermented soya peptide is obtained by placing a soya peptide in a fermenter in the presence of glucose, mineral salts and a given strain of microorganism, under controlled temperature, pH, oxygenation and time conditions. After the fermentation, the fermented soya peptide is obtained by conventional separating and filtering operations. This technique is especially used by the company Coletica which thus sells various fermented plant protein hydrolysates. The fermented or unfermented soya peptides in the composition used according to the present invention preferably have a molecular weight of between about 200 and about 20,000 daltons, as measured, for example, by electrophoresis.

One soya peptide which is particularly preferred for the composition used according to the invention is the fermented peptide known as "Phytokine®" as sold by the company Coletica.

This specific fermented soya peptide, with an average molecular weight of about 800 daltons, is obtained by fermenting a soya peptide with the Lactobaccillus microorganism strain, and its amino acid composition is as follows:

	Number of residues per 100
Hyp.....	0.39
Asp.....	12.64
Thr.....	2.93
Ser.....	4.29
Glu.....	20.08
Pro.....	7.31
Gly.....	7.95

Ala.....	7.76
Cys.....	ND*
Val.....	5.59
Met.....	0.96
Ile.....	4.46
Leu.....	7.42
Tyr.....	1.38
Phe.....	3.39
His.....	2.12
Hyl.....	0.09
Lys.....	5.73
Trp.....	ND*
Arg.....	5.53
βAla.....	ND

(*ND: not determined)

The expression "tripeptide consisting of the amino acids glycine, histidine and lysine" in particular means tripeptides of Gly-His-Lys sequence, the amino acids of which may be in D, L or DL form, which may be conjugated with a carboxylic acid such as acetic acid, in the form of a complex with a metal such as zinc or copper.

Among the tripeptides consisting of the amino acids glycine, histidine and lysine, it is preferred to use the tripeptide "Kollaren-CPP" whose INCI name is "tripeptide-1", as sold by the company Seporga. "Kollaren-CPP" is a tripeptide having the sequence Gly-His-Lys conjugated with acetic acid (acetate) in the form of a complex with zinc.

Thus, more particularly, the present invention relates to a cosmetic method for preventing and/or treating skin stretchmarks, characterized in that the anti-stretchmark agent is chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP®, and mixtures of these peptides.

In the composition used according to the invention, the proportion of anti-stretchmark agent is

between about 0.1% and about 10% by weight relative to the total weight of the composition.

According to one preferred embodiment, the composition used according to the present invention also comprises at least one α-hydroxy acid, in combination with the anti-stretchmark agent. The reason for this is that it has been found, surprisingly, that the joint use of an α-hydroxy acid makes it possible at least to potentiate the activity of the anti-stretchmark agent, if not, in certain cases, to obtain a synergistic effect in preventing and/or treating stretchmarks.

The α-hydroxy acid used according to the invention may be any α-hydroxy acid which produces an exfoliation and/or moisturization effect on the skin, such as, for example, citric acid, pyruvic acid, glycolic acid or lactic acid.

One α-hydroxy acid which is particularly preferred for the composition used according to the invention is lactic acid.

The proportion of α-hydroxy acid is preferably between about 0.1% and about 20% by weight relative to the total weight of the composition.

Preferably, the composition used according to the invention comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP®, and mixtures of these peptides, in combination with lactic acid as α-hydroxy acid. The reason for this is that it has been found that such a combination provides a particularly advantageous effect as regards the anti-stretchmark activity of the composition used according to the invention.

Finally, the composition used according to the invention also advantageously comprises a compound intended to adjust the pH of the composition according to the invention to a value of between about 2 and about 4, and preferably to a value of about 3.5, in particular to partially neutralize the α-hydroxy acid.

In particular, arginine or an alkanolamine such as triethanolamine may be used.

According to one particularly preferred embodiment, the composition used according to the invention also comprises a substance-P and neuropeptide-Y (or NPY hereinbelow) inhibitor compound. This additional compound may be chosen from the substance-P and NPY inhibitor compounds known to those skilled in the art.

However, one substance-P and NPY inhibitor compound that is particularly preferred is a specific extract comprising an active peptide fraction, obtained from green algae (or chlorophycea) known as "*Enteromorpha compressa*" (or "Ao-nori" or "yellow green nori"), such as the product sold by the company Secma under the name "Enteline 2" (INCI name: "butylene glycol, glycerol, *Enteromorpha compressa extract*; CAS No. 92128-82-0).

Specifically, it has been observed that the use of this specific substance-P and neuropeptide-Y inhibitor compound makes it possible to obtain a particularly advantageous tolerance effect of the composition used according to the invention, in particular given the irritant effects of the α-hydroxy acid, in particular of lactic acid.

The proportion of substance-P and NPY inhibitor compound in the composition used according to the invention is preferably between about 0.1% and about 5% by weight relative to the total weight of the composition.

Preferably, the composition used according to the invention comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP® and mixtures of these peptides, in combination with lactic acid and the *Enteromorpha compressa* extract.

The composition used according to the invention also comprises a suitable vehicle, which may be any vehicle among those known to a person skilled in the

art, in order to obtain a cosmetic or dermatological composition which may be used according to the invention, in the form of a cream, a lotion, a gel, an ointment, etc., optionally in the form of an emulsion, also with components known to those skilled in the art for improving, modifying or stabilizing the composition from a cosmetic or dermatological point of view.

In particular, the composition used according to the invention may also comprise compounds contributing secondarily to the anti-stretchmark action, such as the extract of *Sophora japonica* which contributes toward controlling the vascularization of stretchmarks and thus their color, or alternatively silanol compounds such as methylsilanyl lactate, or trace elements based on copper and zinc which are constituents of dermal proteins, such as zinc gluconate and copper gluconate.

The operating conditions for preparing the composition used according to the invention form part of the general knowledge of a person skilled in the art.

Finally, a subject of the present invention is also the use of a composition as defined above to prepare a dermatological medicinal product for preventing and/or treating skin stretchmarks.

The examples which follow are intended to illustrate the present invention and should not in any way be interpreted as restricting its scope.

Example 1 : Anti-stretchmark cream with a pH of 3.5.

	%
- Cetyldimethicone, sold under the name "Albilwax 9801" by the company Goldschmitt	2
- Octyl sebacate	5
- Isononyl isononanoate	7
- Mixture of glyceryl stearate, cetearyl alcohol, cetyl palmitate and cocoglycerides, sold under the name	2.5

"Cutina CBS" by the company Sidobre Sinnova	
- Methyl paraben	0.1
- Propyl paraben	0.1
- Water	qs 100
- PEG 300	5
- Triethanolamine	4.8
- Sepigel 305® (thickener sold by the company SEPPIC)	5.5
- Phytokine®	2
- Lactic acid	10
- Enteline 2®	0.4
- Sophora japonica	3
- Methylsilanyl lactate	3
- Zinc gluconate	0.2
- Copper gluconate	0.2
- Fragrance	0.35

Example 2: Anti-stretchmark cream with a pH of 3.5.

	%
- Cetyldimethicone, sold under the name "Albilwax 9801" by the company Goldschmitt	2
- Octyl sebacate	5
- Isononyl isononanoate	7
- Mixture of glyceryl stearate, cetearyl alcohol, cetyl palmitate and cocoglycerides, sold under the name "Cutina CBS" by the company Sidobre Sinnova	2.5
- Methyl paraben	0.1
- Propyl paraben	0.1
- Water	qs 100
- PEG 300	5
- Triethanolamine	4.8
- Sepigel 305® (thickener sold by the company SEPPIC)	5.5
- Kollaren CPP®	2.5
- Lactic acid	10

- Enteline 2®	0.4
- Sophora japonica	3
- Methylsilanyl lactate	3
- Zinc gluconate	0.2
- Copper gluconate	0.2
- Fragrance	0.35

Example 3 : Clinical study to evaluate the effect of the compositions of Examples 1 and 2 on the regression of stretchmarks, on the basis of an instrumental evaluation combined with a clinical evaluation, after repeated applications to the skin, under the normal conditions of use, for 6 weeks, in 9 adult female volunteers.

1. Object of the study

The object of the present study is to evaluate and compare the effect of the compositions of Examples 1 and 2 above on the "regression" of stretchmarks, by colorimetric measurements of stretchmarks on the skin of the thighs, combined with measurements of biomechanical parameters and with a clinical evaluation, after repeated applications to the skin for 6 weeks, under the normal conditions of use, in 9 adult female volunteers.

2. Relevance of the test

Measurement of the viscoelastic parameters of the skin using a Cutometer® makes it possible to determine the effect of a product on the skin's biomechanical properties, after repeated applications. This apparatus measures the deformation of an area of skin subjected to a mechanical suction stress, and its power of recovery (Wilhelm et al., 1993). Specifically, the viscoelastic properties of the skin are correlated with the notions of suppleness, elasticity and firmness of the tegument.

Measurements using a Chromameter moreover make it possible to evaluate objectively the effect of a

product on skin coloration, in an area with stretchmarks, compared with a control area (normal skin).

When combined with a clinical evaluation on the basis of scores by the Study Director, these instrumental techniques make it possible to evaluate the effect of a product on stretchmarks, in a panel of 9 adult female volunteers, after 6 weeks of twice-daily applications, under the normal conditions of use.

3. Volunteers

9 panel members were finally accepted by the Study Director on the basis of a clinical examination specific to the study, carried out just before the start of the trial. They all participated in the entire trial.

The analysis of the results was thus made on a panel of 9 adult female volunteers (or 8 for the colorimetric measurements) from 20 to 31 years old (average age: 26 years old), showing stretchmarks dating back less than 8 months.

4. Protocol

4.1 Initial clinical and instrumental evaluations:

4.1.1. Determination of the viscoelastic parameters:

These parameters were evaluated on the skin of both thighs using a Cutometer™ (Courage + Khazaka, Germany), on two diametrically opposite areas, delimited on the left and right thighs of each of the adult female volunteers specifically selected and recruited to carry out and objectivize this type of trial. These measurements were taken on an area showing stretchmarks, and also on an adjacent area without stretchmarks ("normal skin"), after marking the areas using a transparent plastic card bearing anatomical markers.

4.1.2. Coloration measurement

The evaluation of the coloration of a stretchmark was carried out on the skin of both thighs and of an adjacent control area (free of stretchmarks) by analysis of the clarity variable "L*" and the chromaticity coordinates "a*" and "b*", using a CR 321 Chromameter (Minolta) fitted with a cone for colorimetric measurements on an area 3 mm in diameter.

These measurements were carried out after a rest period of about 20 minutes, in an air-conditioned room with an ambient temperature maintained at 22 ± 2°C and a relative humidity of 50 ± 5%, by means of a microprocessor connected to temperature and humidity sensor-transmitters so as to achieve a stable equilibrium of water exchange between the skin of each panel member and the surrounding environment. The stability of these parameters was monitored and printed out continuously using a multipath recorder.

4.1.3. Clinical evaluation

The following judgement criteria were evaluated, by the Deputy Study Director, on the basis of 9-point clinical scores (1 to 9), on both thighs, for each of the volunteers:

· size of the stretchmarks,
· color of the stretchmarks,
· relief of the stretchmarks.

4.1.4. Photographs

Color macrophotographs of an area of skin of each thigh were taken, using a Nikon F-801S camera fitted with a Nikon 105MM macro objective lens, under lighting of "daylight" type (6500° K).

4.2. Determination of the efficacy of the products after repeated applications

4.2.1. Application methods

The products studied were applied twice a day for 6 consecutive weeks, under the normal conditions of use, by the volunteer herself at home, on the skin of both thighs (1 product for each thigh according to a randomization - binomial law).

In order to achieve the maximum standardization of the study conditions, the products studied were applied once a week, in the presence of the laboratory staff.

4.2.2. Effect on the viscoelastic properties of the skin (tonicity, firmness, suppleness, elasticity)

The viscoelastic parameters of the skin of both thighs (areas with and without stretchmarks) marked out accurately relative to the first day of the test and according to the same principle, were determined after the sixth week of use of the products. This evaluation was carried out 16 to 24 hours after the last application of the products, by the laboratory staff, so as to specifically measure the variations in the elastic parameters of the skin tissue that are induced by the repeated uses.

4.2.3. Effect on the coloration of the skin

The skin coloration measurements were carried out using a Chromameter® after the 6 weeks of use, on the areas determined during the first day of the study and accurately marked out, according to the same principle (areas with and without stretchmarks).

4.2.4. Clinical evaluations and self-evaluations

The evaluations of the skin of both thighs were carried out by the Study Director, on the basis of 6-point clinical scores, according to the same principle as that followed during the initial determination, after the 6 weeks of application.

4.2.5. Photographs

Color macrophotographs of the areas determined during the first day of the study and accurately marked out were taken, according to the same principle, after the 6 weeks of application.

4.3. Analysis and interpretation of the results

4.3.1. Biomechanical parameters

- The mean values of the viscoelastic parameters determined on D1 and D43 on the 2 thighs (areas with stretchmarks and areas without stretchmarks) were calculated by determining the arithmetic mean and the error obtained relative to the mean (S.E.M.) of the individual measurements taken on all of the panel members.

- The initial values obtained on the right and left thighs (before the first application of the products) were compared by an analysis of variance (ANOVA, significance: $p < 0.05$).

- The values obtained after using the products for 6 weeks were compared with the initial values, determined before the first application, by the paired serial Student "t" test ("one-tail", significance: $p < 0.05$), for each of the areas (right and left thighs, areas with and without stretchmarks).

- The effects obtained on the right and left thighs (areas with and without stretchmarks) were compared by an analysis of variance (ANOVA, significance: $p < 0.05$) and by the multiple comparison test ("L.S.D."), relating to the differences calculated between the values acquired after the 6 weeks of use and the initial values (ΔD43-D1).

- The mean variation percentages of the parameters evaluated during the trial were calculated for each area of skin, after the 6 weeks of application, relative to the initial value, starting with the mean values obtained for all of the panel members.

4.3.2. Colorimetric measurements

- The mean values of the colorimetric parameters, determined at each stage of the study, were calculated by determining the arithmetic mean and the error relative to the mean (S.E.M.) of the individual measurements taken on all of the panel members.

These determinations relate to the clarity variable "L*", the chromaticity coordinates "a*" and "b*" and the Individual Typological Angle ITA°, calculated according to the following formula:

$$ITA° = [\text{arc tangent } (L^* - 50)/b^*]180/3,14159$$

- The initial values obtained on the right and left thighs (before the first application of the products) were compared by an analysis of variance (ANOVA, significance: $p < 0.05$).

- The values obtained after using the products for 6 weeks were compared with the initial values, determined before the first application, by the paired serial Student "t" test ("one-tail", significance: $p < 0.05$), for each of the areas (right and left thighs, areas with and without stretchmarks).

- The effects obtained on the right and left thighs (areas with and without stretchmarks) were compared by an analysis of variance (ANOVA, significance: $p < 0.05$) and by the multiple comparison test ("L.S.D."), relating to the differences calculated between the values acquired after the 6 weeks of use and the initial values ($\Delta D43-D1$).

- The mean variation percentages of the parameters evaluated during the trial were calculated for each area of skin, after the 6 weeks of application, relative to the initial value, from the mean values obtained for all of the panel members.

4.3.3. Clinical scores

- The mean values of the judgement criteria determined at each stage of the study on the basis of the clinical scores were calculated by determining the

arithmetic mean and the standard deviation (Sd) of the individual data acquired for all of the panel members.

- The values obtained, after applying the products, were compared with the values determined during the first day of the trial (initial evaluations) by the paired serial Wilcoxon test ("one-tail", significance: $p < 0.05$), for each area treated.

- The effect of the products was compared by a paired serial Wilcoxon test ("one-tail", significance: $p < 0.05$) relating to the values obtained before and after repeated applications.

- The mean variation percentages of each of the evaluation criteria were calculated relative to the initial data, starting with the mean values obtained for all of the volunteers.

5. Results and conclusion

5.1. Cutometric measurements

The statistical analysis previously demonstrated that the initial values of the biomechanical parameters were identical, firstly on each of the areas without stretchmarks, and secondly on each of the areas with stretchmarks. Statistically significant differences were moreover revealed between the areas with and without stretchmarks, reflecting a skin which is slacker and less elastic in the areas with stretchmarks.

5.1.1. Anti-stretchmark cream of Example 1

The analysis of the results made it possible to reveal, after 6 weeks of application, relative to the initial measurement:

- On the area without stretchmarks:

· a tendency toward decreasing the Uf (final elongation), by about 4% during the 1st and 3rd stress,

· a statistically significant decrease in Uv/Ue (degree of viscoelasticity determining the size of the viscous

response relative to the elastic response), of about 14%.

- On the area with stretchmarks:

· a tendency toward decreasing the Uf (final elongation), by about 2% during the 1st and 3rd stress,

· a stabilization of Ua/Uf (degree of recovery after stress),

· a statistically significant decrease in Uv/Ue (degree of viscoelasticity determining the size of the viscous response relative to the elastic response) of about -17%.

A significant improvement in the firmness and tonicity components is thus found, on the area with stretchmarks.

5.1.2. Anti-stretchmark cream of Example 2

The analysis of the results made it possible to reveal, after 6 weeks of application, relative to the initial measurement:

- On the area without stretchmarks:

· a statistically significant decrease in Uf (final elongation), of about 6% during the 1st and 3rd stress,

· a stabilization in Ua/Uf (degree of recovery after stress),

· a stabilization of Uv/Ue (degree of viscoelasticity).

- On the area with stretchmarks:

· a tendency toward decreasing the Uf (final elongation), by about 2% during the 1st stress,

· a stabilization of Ua/Uf (degree of recovery after stress),

· a tendency toward decreasing the Uv/Ue (degree of viscoelasticity), by about 9%.

A marked tendency (non-significant for the 9 panel members) toward improving the tonicity and firmness components of the skin in the area with stretchmarks is thus found.

5.2. Colorimetric measurements

The statistical analysis previously demonstrated that the initial values of the colorimetric parameters were identical, firstly on each of the areas without stretchmarks, and secondly on each of the areas with stretchmarks. It should be noted that the skin of the areas with stretchmarks (before and after using the products for 6 weeks) was paler than that of the areas without stretchmarks (higher clarity variable L* and higher I.T.A.°).

No favorable and statistically significant improvement in the colorimetric parameters was recorded, after using each of the products, irrespective of the areas (with and without stretchmarks).

5.3. Clinical evaluations by the Study Director

The analysis of the results made it possible to reveal a statistically significant improvement in the following criteria, with the exception of the length of the stretchmarks. A significant difference was moreover noted between the two products studied for this criterion, reflecting a greater regression of stretchmarks on the area treated with the anti-stretchmark cream of Example 2.

	Anti-stretchmark cream Example 1	Anti-stretchmark cream Example 2
Width of the stretchmarks (thin → broad)	-17%*	-14%
Length of the stretchmarks (short → long)	-8%	-14%•
Color of the stretchmarks (abnormal → normal)	-18% (tendency close to the significant level)	-26%*
Relief of the stretchmarks (hollow/puffy → normal)	-26%*	-16%*

* statistically significant value at time 6 weeks, relative to the initial evaluation

• statistically significant decrease compared with the anti-stretchmark cream of Example 1 (Wilcoxon test, "one-tail").

5.4. Tolerance of the cosmetic product assessed by the volunteer

- Skin sensations experienced:

  · none: 100%

- Best-tolerated product:

  · no difference: 100%

No pathological irritation reaction significant of a skin intolerance was noted. The 9 volunteers also

indicated that they did not observe any irritation and/or discomfort sensations during the trial.

6. Conclusion

In conclusion, the anti-stretchmark creams of Examples 1 and 2, which differ from each other only in the anti-stretchmark active agent used, applied for 6 consecutive weeks under the normal conditions of use, to 9 adult female volunteers, made it possible to obtain a regression of stretchmarks, demonstrated by instrumental methods and on the basis of clinical scores.

This effect is reflected:

- for the cream of Example 1 (use of "Phytokine®"):
  - · by a statistically significant improvement in the tonicity and firmness components of the skin;
  - · by statistically significant regression of the width of the stretchmarks (-17%) and of their relief (-26%), with a non-significant tendency on their color (-18%);
- for the cream of Example 2 (use of "Kollaren-CPP®"):
  - · by a marked, non-significant tendency toward improving the tonicity and firmness components of the skin;
  - · by a statistically significant decrease in the length of the stretchmarks, compared with the cream of Example 1;
  - · by a statistically significant improvement in the color (-26%) and the relief (-16%) of the stretchmarks.

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- Wilhelm K.P., Cua A.B. and Maibach H.I. In vivo study on age-related elastic properties of Human skin. In "Noninvasive Methods for the Quantification of skin Functions: An Update on Methodology and clinical Applications". Frosch P.J. and Kigman A.M. Ed., Springer-Verlag, 1993: 190-203.

CLAIMS

1. Cosmetic method for preventing and/or treating skin stretchmarks, characterized in that a composition is applied to the areas of skin liable to form or comprising stretchmarks, this composition comprising, in a suitable vehicle, at least one anti-stretchmark agent chosen from the group consisting of soya peptides and tripeptides consisting of the amino acids glycine, histidine and lysine, and mixtures of these peptides.

2. Cosmetic method for preventing and/or treating stretchmarks according to Claim 1, characterized in that a composition is applied to the areas of skin liable to form or comprising stretchmarks, this composition comprising, in a suitable vehicle, at least one anti-stretchmark agent chosen from the group consisting of fermented soya peptides and tripeptides consisting of the amino acids glycine, histidine and lysine, and mixtures of these peptides.

3. Cosmetic prevention and/or treatment method according to Claim 1 or 2, characterized in that the anti-stretchmark agent is chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP®, and mixtures of these peptides.

4. Cosmetic prevention and/or treatment method according to any one of Claims 1 to 3, characterized in that the proportion of anti-stretchmark agent is between about 0.1% and about 10% by weight relative to the total weight of the composition.

5. Cosmetic prevention and/or treatment method according to any one of Claims 1 to 4, characterized in that the composition also comprises at least one α-hydroxy acid, in combination with the anti-stretchmark agent.

6. Cosmetic prevention and/or treatment method according to Claim 5, characterized in that the α-hydroxy acid is lactic acid.

7. Cosmetic prevention and/or treatment method according to Claim 5 or 6, characterized in that the proportion of α-hydroxy acid is between about 0.1% and about 20% by weight relative to the total weight of the composition.

8. Cosmetic prevention and/or treatment method according to any one of the preceding claims, characterized in that the composition comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP® and mixtures of these peptides, in combination with lactic acid.

9. Cosmetic prevention and/or treatment method according to any one of the preceding claims, characterized in that the composition also comprises a compound for adjusting the pH to a value of between about 2 and about 4.

10. Cosmetic prevention and/or treatment method according to any one of the preceding claims, characterized in that the composition also comprises at least one substance-P and neuropeptide-Y inhibitor compound.

11. Cosmetic prevention and/or treatment method according to Claim 10, characterized in that the substance-P and neuropeptide-Y inhibitor is the extract of *Enteromorpha compressa*.

12. Cosmetic prevention and/or treatment method according to Claim 10 or 11, characterized in that the proportion of substance-P and neuropeptide-Y inhibitor compound is between about 0.1% and about 5% by weight relative to the total weight of the composition.

13. Cosmetic prevention and/or treatment method according to any one of the preceding claims, characterized in that the composition comprises an anti-stretchmark agent chosen from the group consisting of the soya peptide Phytokine® and the tripeptide Kollaren-CPP® and mixtures of these peptides, in combination with lactic acid and *Enteromorpha compressa* extract.

14. Cosmetic prevention and/or treatment method according to any one of the preceding claims, characterized in that the composition also comprises at least one compound chosen from the group consisting of extract of *Sophora japonica*, methylsilaryl lactate, copper gluconate and zinc gluconate, and mixtures of these compounds.

15. Use of a composition as defined in any one of Claims 1 to 14, to prepare a dermatological medicinal product for preventing and/or treating skin stretchmarks.

Docket No. _____

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Cosmetic method for preventing and/or treating skin stretchmarks, and use in dermatology

the specification of which is attached hereto unless the following box is checked:

☒ was filed on October 5th, 1999 as ~~United States Application Number or~~ PCT International Application Number PCT/FR/99/02375 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
98/12435	FRANCE	5/10/1998	YES

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

APPLICATION NO.	FILING DATE

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Bent, Reg. No. 29,768; David A. Blumenthal, Reg. No. 26,257; William T. Ellis, Reg. No. 26,874; John J. Feldhaus, Reg. No. 28,822; Patricia D. Granados, Reg. No. 33,683; John P. Isacson, Reg. No. 33,715; Donald D. Jeffery, Reg. No. 19,980; Eugene M. Lee, Reg. No. 32,039; Richard Linn, Reg. No. 25,144; Peter G. Mack, Reg. No. 26,001; Brian J. McNamara, Reg. No. 32,789; Sybil Meloy, Reg. No. 22,749; George E. Quillin, Reg. No. 32,792; Colin G. Sandercock, Reg. No. 31,298; Bernhard D. Saxe, Reg. No. 28,665; Charles F. Schill, Reg. No. 27,590; Richard L. Schwaab, Reg. No. 25,479; Arthur Schwartz, Reg. No. 22,115; Harold C. Wegner, Reg. No. 25,258.

Address all correspondence to FOLEY & LARDNER, Washington Harbour, 3000 K Street, N.W., Suite 500, P.O. Box 25696, Washington, D.C. 20007-8696. Address telephone communications to _____ at (202) 672-5300.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor	Signature of First or Sole Inventor	Date
MSIKA Philippe		March 28, 2001
Residence Address **226, rue Marcadet 75008 Paris FRANCE**		Country of Citizenship **FRANCE**
Post Office Address **Same as above**		

Full Name of Second Inventor	Signature of Second Inventor	Date
Residence Address		Country of Citizenship
Post Office Address		

Full Name of Third Inventor	Signature of Third Inventor	Date
Residence Address		Country of Citizenship
Post Office Address		

Full Name of Fourth Inventor	Signature of Fourth Inventor	Date
Residence Address		Country of Citizenship
Post Office Address		

Full Name of Fifth Inventor	Signature of Fifth Inventor	Date
Residence Address		Country of Citizenship
Post Office Address		

Atty. Docket. No. 065691/0215

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Philippe Msika

Entitled: COSMETIC METHOD FOR PREVENTING AND/OR TREATING SKIN STRETCHMARKS, AND USE IN DERMATOLOGY

Serial No.: To be assigned

Filing Date: April 5, 2001

ASSOCIATE POWER OF ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned attorney of record hereby appoints Stephen B. Maebius, Registration No. 35,264 as an associate attorney with full power of association, substitution and revocation, to prosecute the above-identified application and transact all business in the Patent and Trademark Office connected therewith.

Respectfully submitted,

Date April 5, 2001

By _____

FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5571
Facsimile: (202) 672-5399

Harold C. Wegner
Attorney for Applicant
Registration No. 25,258

United States Patent & Trademark Office

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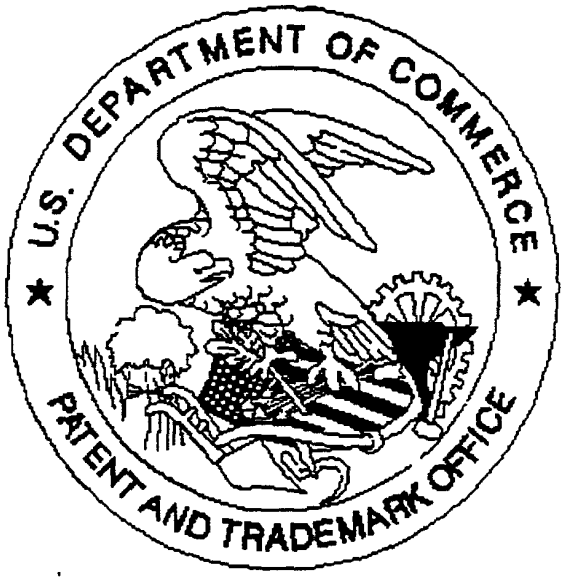

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